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Subject: 1-year Pediatric Exclusivity Postmarketing Adverse Event
Review

Drug Name(s): Lamotrigine (Lamictal)

Pediatric Exclusivity
Approval Date: Feb 14, 2007

Application
Type/Number: NDA 20-241, 1994

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2007-388

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EXECUTIVE SUMMARY

Lamotrigine has been labeled to treat seizures in pediatric patients for 10 years and, specifically, in patients 2 years old and older for 5 years. These approvals were based on clinical trials and lamotrigine is extensively labeled for use in pediatric patients based on the trial data. Labeling includes a Black Box Warning and a bolded warning for serious skin adverse events and warnings for hypersensitivity reactions, multi-organ failure, and blood dyscrasias. According to lamotrigine labeling, any of these adverse events except blood dyscrasias can include rash, failure of various organs, or death. Also according to labeling, serious skin events had a higher incidence in pediatric patients than in adult patients in clinical trials.

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of lamotrigine in pediatric patients. Up to the search date of June 23, 2008, AERS contained 14,255 reports for lamotrigine (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 13% of the total (1787/14,255).

DPV was asked to focus on the 1-year period following the approval of pediatric exclusivity, February 14, 2007 to February 14, 2008. We used an AERS data lock date of March 14, 2008, to allow time for reports received up to February 14, 2008, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 3306 reports (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 9% of the total (303/3306). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

All reports of death in pediatric patients since marketing approval were given hands-on review and are summarized. In addition, we performed hands-on review of all pediatric reports of hepatotoxicity received since May 1, 2006, the data cut-off date of the December 2006 DPV review of hepatotoxicity with lamotrigine, and all pediatric reports of blood dyscrasia, hypersensitivity reactions, and multi-organ failure received in the pediatric exclusivity period. Characteristics of pediatric rash reports received during the pediatric exclusivity period are presented as extracted from AERS, without hands-on review.

OPT also expressed particular interest in the issue of increased incidence of respiratory illness or infection in pediatric patients receiving lamotrigine. No unusual respiratory adverse events were found in this review that could not be related to other factors in the reports. Also, because of the limitations of AERS for analyzing high-background events, this review cannot support or refute an increased incidence of respiratory illness or infection in pediatric patients receiving lamotrigine.

No new safety issues were identified by this review and the profiles of adverse events identified in this review conform to those previously identified and labeled. Continued routine monitoring is recommended.

1 BACKGROUND

Lamotrigine is an anticonvulsant agent marketed by GlaxoSmithKline. The two dosage forms, Lamictal (tablet) and Lamictal CD (chewable-dispersible tablet), received FDA approval on December 27, 1994 and August 24, 1998, respectively. In 1998, lamotrigine was approved for the adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients. In 2003, lamotrigine was approved for the adjunctive treatment of partial seizures in adult and pediatric patients equal to or greater than 2 years of age. Also in 2003, the Lennox-Gastaut indication was modified to specify approval in pediatric patients equal to or greater than 2 years of age. In 2006, lamotrigine was approved as adjunctive treatment of primary generalized tonic-clonic seizures in adults and pediatric patients. Additionally, lamotrigine is approved for maintenance treatment of Bipolar I Disorder and conversion to monotherapy to treat partial seizures in adults. Pediatric exclusivity was granted on February 14, 2007.

The effectiveness of lamotrigine as adjunctive therapy in pediatric patients with partial seizures was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged 2 to 16 years (n = 98 on lamotrigine, n = 101 on placebo). The effectiveness of lamotrigine as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on lamotrigine, n = 90 on placebo). The effectiveness of lamotrigine as adjunctive therapy in patients with primary generalized tonic-clonic seizures was established in a multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥ 2 years (n = 58 on lamotrigine, n = 59 on placebo).

Thus, lamotrigine has been studied in placebo-controlled trials in pediatric patients. As a result, lamotrigine has been approved and labeled for use in pediatric patients for 10 years and specifically approved and labeled for use in patients as young as 2 years old for 5 years. Because of this extensive history and the FDA's receipt of over 300 pediatric adverse event reports in the 1-year pediatric exclusivity period, hands-on review of adverse event reports for the year was limited to the adverse events identified by OPT as areas of focus and to in utero exposures. All reports of death in pediatric patients since approval were given hands-on review. Also, the numbers of adverse event reports in various pediatric age groups and adults was compared to usage of lamotrigine in these age groups to look for disproportional reporting.

1.1 PREVIOUS OSE POST-MARKETING REVIEWS:

- December 29, 2006. A review of hepatotoxicity reported with lamotrigine found that liver failure has been reported with lamotrigine without overt signs of hypersensitivity or involvement of other organs. Lamotrigine labeling includes warnings about hypersensitivity reactions and acute multi-organ failure that may include various degrees of hepatic failure.¹

¹ Phelan K. Lamotrigine hepatotoxicity. FDA Postmarketing Safety Review. December 29, 2006.

- February 1, 2005. Review of brady- and tachyarrhythmias reported with lamotrigine found a possible association between lamotrigine and bradycardia.²
- July 16, 2003. A review of hepatotoxicity reported with lamotrigine concluded that the labeling of hepatic failure within the context of hypersensitivity reactions and multi-organ failure adequately described the cases that were reviewed.³
- December 22, 2000. A review of serious skin reactions reported with lamotrigine in pediatric patients over a 2.5 year time period found reported cases to be consistent with lamotrigine labeling.⁴
- October 23, 2000. Review of aplastic anemia, pancytopenia, bone marrow disorders, thrombocytopenia, neutropenia, ecchymosis, red cell aplasia, and lymphadenopathy reported with lamotrigine recommended more prominent labeling of aplastic anemia, neutropenia, and pancytopenia.⁵

1.2 PRODUCT FORMULATIONS AND INDICATIONS

Lamotrigine is available in two formulations.

- Lamictal tablet approved December 27, 1994 (NDA 20-241) and available in 25 mg, 100 mg, 150 mg, and 200 mg strengths.
- Lamictal CD, chewable-dispersible tablet approved August 24, 1998 (NDA 20-764) and available in 2 mg, 5 mg, and 25 mg strengths.

Lamotrigine is indicated as

- adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients greater than or equal to 2 years of age
- conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug
- maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy

² Sanders, D. Lamotrigine brady- and tachyarrhythmias. FDA Postmarketing Safety Review. February 1, 2005.

³ Pratt R. Lamotrigine acute liver failure. FDA Postmarketing Safety Review. July 16, 2003.

⁴ Thambi L. Lamotrigine and skin reactions with serious outcomes in pediatric patients from January 1, 1998 through June 30, 2000. December 22, 2000.

⁵ Mease M. Lamotrigine and aplastic anemia, pancytopenia, bone marrow disorders, thrombocytopenia, neutropenia, ecchymosis, red cell aplasia, and lymphadenopathy. October 23, 2000.

1.3 PEDIATRIC LABELING⁶

Lamotrigine has been approved for use in pediatric patients for 10 years and pediatric labeling is extensive. The following list of excerpts is not exhaustive.

From the black-box warning:

- serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of Lamictal. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (age <16 years) receiving Lamictal as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy.
- In a prospectively followed cohort of 1,983 pediatric patients with epilepsy taking adjunctive Lamictal, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

From Pharmacokinetics and Drug Metabolism section:

- Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED [antiepileptic drug] therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing more than 30 kg being administered the same AEDs. These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

From Clinical Studies section:

- The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged 2 to 16 years (n = 98 on LAMICTAL, n = 101 on placebo).
- The effectiveness of LAMICTAL as adjunctive therapy in patients with primary generalized tonic-clonic seizures was established in a multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥ 2 years (n = 58 on LAMICTAL, n = 59 on placebo).

⁶ Lamictal Prescribing Information. GlaxoSmithKline. 2005.

- The effectiveness of LAMICTAL as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on LAMICTAL, n = 90 on placebo).

From Warnings section:

- The incidence of serious rash associated with hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983 patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience.
- There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared to 0.6% (6 of 952) patients not taking valproate.
- Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial cause.
- Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with LAMICTAL was discontinued.

From Precautions section:

- Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder has not been established.

From Adverse Reactions section:

- The most commonly observed ($\geq 5\%$) adverse experiences seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients and not seen

at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

- In 339 patients age 2 to 16 years with partial seizures or generalized seizures of Lennox- Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL and deterioration of seizure control for patients treated with placebo.
- Approximately 11.5% of the 1,081 pediatric patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

The AERS database was searched for all reports with lamotrigine as a suspect drug with the following additional criteria:

- Search date June 23, 2008
 - Adults (aged 17 to 105 years)
 - received since approval date (no date restrictions)
 - received during pediatric exclusivity period (February 14, 2007 to March 14, 2008)
 - Null (unknown) age
 - received since approval date (no date restrictions)
 - received during pediatric exclusivity period (February 14, 2007 to March 14, 2008)
- Pediatric patients (aged 0 to 16 years)
 - Search date June 23, 2008
 - received since approval date (no date restrictions)
 - Search date June 23, 2008
 - received during pediatric exclusivity period (February 14, 2007 to March 14, 2008)
 - Search date June 23, 2008
 - received since approval date (no date restrictions) AND
 - outcome death
 - Search date August 7, 2008
 - received since May 1, 2006, estimated AERS data cut-off date for DPV December 2006 review of hepatotoxicity with lamotrigine, AND
 - MedDRA high level terms (HLT) and preferred terms (PT): hepatic failure and associated disorders (HLT), hepatic fibrosis and cirrhosis (HLT), hepatic necrosis (PT), hepatitis fulminant (PT), liver transplant

(PT), hepatitis acute (PT), hepatitis (PT), hepatocellular damage (PT), hepatotoxicity (PT)

Results of all searches were exported to Excel, which was used for all data manipulation and extraction for this document. The list of tables below describes how the data were extracted and identifies the AERS search from the above list that provided the data for each table.

In addition to a general overview of the AERS data, OPT asked DPV to focus on hepatotoxicity, hypersensitivity reactions, multi-organ failure, blood dyscrasias and rashes. OPT also expressed interest in increased respiratory infection or illness in pediatric patients. In addition, DPV reviewed cases of pediatric death and in utero exposure.

Based on the pediatric death cases, the lamotrigine NDA approval packages were searched in PharmaPendium⁷ for information on cardiac effects.

2.2 DATA SELECTION FOR TABLES IN SECTION 3 AERS RESULTS FOR LAMOTRIGINE

Cases in the areas of special focus were identified by several methods and data were extracted by hands-on review of each case or by reviewing aggregate data as entered into AERS and exported to Excel.

- Tables 1, 2, and 3 contain AERS crude report counts derived from the adult and null-age searches and the first two pediatric searches listed above. Duplicate reports were not removed. Table 3 also shows domestic usage data, obtained from Verispan, by age group for a time period that mostly overlaps the pediatric exclusivity period.
- Tables 4, 5, and 6 contain case series characteristics of all 303 pediatric AERS reports received in the pediatric exclusivity period and retrieved by the second pediatric search above. These characteristics were derived from aggregate report data and not from hands-on case review, so duplicate reports were not removed. Labeling status of the most frequently reported adverse events in the 303 reports is presented in Table 5. Labeling status of the most frequently reported adverse events in the 172 reports among the 303 that reported a serious outcome is presented in Table 6.
- Table 7 contains characteristics extracted through hands-on case review of hepatotoxicity cases from the last pediatric search listed above. Duplicate reports were removed.
- Tables 8 and 9 contain characteristics of hypersensitivity and blood dyscrasia cases, respectively, extracted through hands-on case review. Duplicate reports were removed. Cases were identified by skimming the narratives of the 303 pediatric reports received in the pediatric exclusivity period, which were retrieved from AERS using the second search listed under pediatrics, above. Because labeling describes both of these adverse events in the context of rash, any report that reported rash is included with rash reports.

⁷ PharmaPendium™ is an Elsevier product that contains indexed and searchable drug information including FDA drug approval packages.

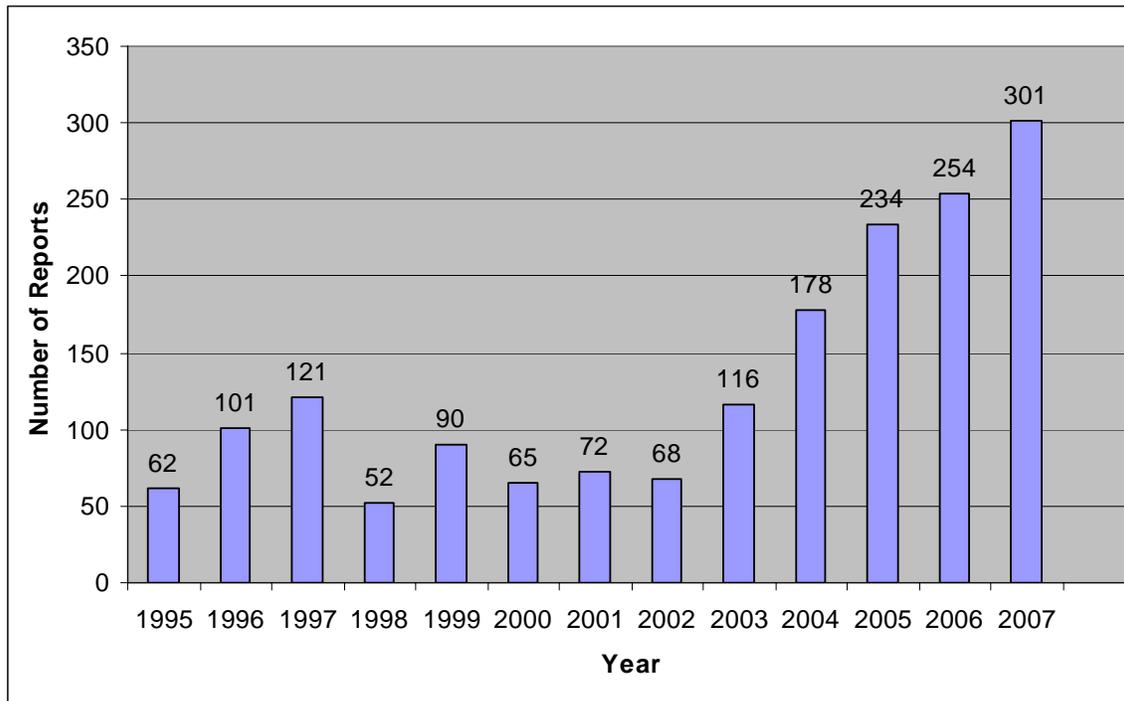
- Table 10 contains characteristics of rash reports. The characteristics were extracted from data as entered into AERS and exported to Excel and not from hands-on case review. Duplicate reports were not removed. Rash cases were identified by skimming the narratives of the 303 pediatric reports received in the pediatric exclusivity period, which were retrieved from AERS using the second search listed under pediatrics, above. Any report that mentioned rash, even if it included one of the other focus events, was included with rash reports, because all of the other focus events appear in labeling in the context of rash. There were no multi-organ failure cases that did not also include rash, so there is no separate table of multi-organ failure cases.
- Table 11 contains results of hands-on review of in utero lamotrigine exposure cases received in the pediatric exclusivity period. In utero exposure cases were identified by skimming the narratives of the 303 pediatric reports received during the pediatric exclusivity period. These were retrieved by the second search listed above under pediatrics. Duplicate reports were removed.
- Table 12 contains characteristics of pediatric reports with an outcome of death. All reports of death in pediatric patients entered into AERS from lamotrigine approval to the search date of June 23, 2008 were retrieved by the third pediatric search listed above and reviewed individually. Among 106 AERS reports retrieved, 83 unique cases remained after duplicate removal.

3 AERS RESULTS FOR LAMOTRIGINE

3.1 COUNT OF REPORTS: ALL SOURCES - US AND FOREIGN - FROM MARKETING APPROVAL

Table 1: Crude counts¹ of AERS Reports from All Sources from Marketing Approval to the AERS Search Date (December 27, 1994 to June 23, 2008)			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	8100 (5957)	5055 (3069)	572 (307)
Pediatrics (0-16 yrs.)	1787 (1193)	1250 (639)	106 (30)
Age unknown (Null values)	4368 (3601)	1905 (1146)	161 (69)
Total	14,255 (10,751)	8210 (4854)	839 (406)
¹ May include duplicates			
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious.			

Figure 1: Reporting trend for pediatric reports since approval date



3.2 COUNT OF REPORTS: ALL SOURCES - US AND FOREIGN - DURING PEDIATRIC EXCLUSIVITY PERIOD (FEBRUARY 14, 2007 TO MARCH 14, 2008)

Table 2: Crude Counts¹ of AERS Reports from All Sources During Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008)			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1898 (1550)	1060 (713)	159 (136)
Pediatrics (0-16 yrs)	303 (234)	172 (105)	2 (2)
Age unknown (Null Values)	1105 (976)	431 (302)	18 (10)
Total	3306 (2760)	1663 (1120)	179 (148)

¹ May include duplicates

² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious.

3.3 COUNT OF REPORTS: ALL SOURCES – US AND FOREIGN - DURING PEDIATRIC EXCLUSIVITY PERIOD (FEBRUARY 14, 2007 TO MARCH 14, 2008) STRATIFIED BY AGE WITH DOMESTIC REPORT NUMBERS AND DOMESTIC DRUG USAGE DATA

Table 3. Crude Counts¹ of AERS Reports Received During Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) Broken Down by Age Group and Source with Domestic Drug Use Data for the Same Age Groups and Time Period			
Age Group	Total Adverse Event Reports (%) (n = 4661)	Domestic Adverse Event Reports (%) (n=2755)	Domestic Drug Use – Total Patients² (%) March 2007 through February 2008
0 through 1 year	135 (2.9%)	6 (5 in utero, 1 breast milk exposure) (0.2%)	36 (0%)
2 through 5 years	281 (6.0%)	21 (0.8%)	1,192 (0.2%)
6 through 11 years	555 (11.9%)	71 (2.6%)	11,507 (2.1 %)
12 through 16 years	687 (14.7%)	131 (4.8%)	27,736 (5.2%)
17 years and older	1898 (40.7%)	1550 (56.3%)	493,003 (91.9%)
unknown age	1105 (23.7%)	976 (35.4%)	3,461 (0.6%)
Total	4661 (100%)	2755 (100%)	536,613 (100%)
<p>¹ May include duplicates</p> <p>² Projected number of patients receiving a prescription for lamotrigine dispensed by U.S. retail pharmacies March 2007 through February 2008. Source: Verispan Vector One: National, Extracted 6-2008, 2007-388 TPT Lamotrigine.</p>			

**3.4 CASE CHARACTERISTICS FROM ONE-YEAR PEDIATRIC EXCLUSIVITY PERIOD
(FEBRUARY 14, 2007 TO MARCH 14, 2008) REVIEW**

Table 4: Characteristics of Pediatric Reports Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) [N=303, may include duplicates]			
Gender [n=293]	Male (130) Female(163)		
Age [n=281]	0- <1 month (4) 1 month <2 yrs (17) 2-5 yrs (28) 6-11 yrs (92) 12-16 yrs (140) Median 10 years; Range 1 hour to 16 years		
Origin [n=301]	US (236), Foreign (65)		
Event date [n=208]	1996 (1) 1997 (1) 2003 (2)	2004 (6) 2005 (21) 2006 (105)	2007 (69) 2008 (3)
Indication [n=263]	seizures / convulsions / epilepsy (144) absence seizure (4) bipolar disorder / mania / hypomania (80) emotional lability / mood disorder (15) depression / depressive disorder (5) schizoaffective disorder (2) attention deficit / hyperactivity disorder (3) aggression / anger (2) chronic encephalopathy (1) migraine (1) accidental exposure (1) accidental overdose (1) deliberate poisoning (1) drug exposure during pregnancy (3)		
Most serious outcome selected on MedWatch form [n=172]	Death (2), Life-Threatening (17), Hospitalization (67) Disability (8), Congenital Anomaly (8), and Other Serious (70)		

The following two tables show the labeling status of adverse events reported in at least 1.7% of the 303 pediatric cases received during the post-exclusivity period and in the subset of 172 pediatric cases with a serious outcome. Both of these tables are based on crude AERS data that may include duplicate reports. Certain adverse events, such as drug ineffective or drug exposure during pregnancy, are not appropriate to label, because they can occur with any drug and they are nonspecific. These are described as not applicable in the tables.

Table 5: Crude Counts and Labeling Status of Adverse Events Reported in at Least 5 (1.7%) of the 303 Pediatric Cases Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) (May include duplicates)

Rank	Preferred Term (PT)	Count	Label Status
1	rash	58	Black box warning
2	convulsion	45	Indication
3	drug ineffective	22	not applicable ¹
4	Stevens-Johnson Syndrome	18	Warnings
5	vomiting	16	Adverse Reactions
6	drug exposure during pregnancy	15	not applicable
7	headache	14	Adverse Reactions
8	pyrexia	13	Adverse Reactions (“fever”)
9	rash generalized	12	Black box warning
10	drug interaction	12	not applicable
11	<i>abnormal behavior</i>	11	<i>not labeled</i>
12	somnolence	10	Adverse Reactions
13	irritability	10	Adverse Reactions
14	tremor	8	Adverse Reactions
15	<i>pruritus</i>	8	<i>not labeled</i>
16	nausea	7	Adverse Reactions
17	malaise	7	Adverse Reactions
18	diarrhea	7	Adverse Reactions
19	coordination abnormal	7	Adverse Reactions
20	rash maculo-papular	6	Adverse Reactions
21	pharmaceutical product complaint	6	not applicable
22	overdose	6	Overdosage
23	lymphadenopathy	6	Warnings (under hypersensitivity reactions)
24	fatigue	6	Adverse Reactions
25	drug toxicity	6	not applicable
26	<i>aggression</i>	6	<i>not labeled</i>
27	viral infection	5	Adverse Reactions (“infection”)
28	urticaria	5	Adverse Reactions
29	toxic epidermal necrolysis	5	Black box warning

Rank	Preferred Term (PT)	Count	Label Status
30	personality change	5	Adverse Reactions ("personality disorder")
31	medication error	5	not applicable
32	insomnia	5	Adverse Reactions
33	epistaxis	5	Adverse Reactions
34	epilepsy	5	Indication
35	complex partial seizures	5	Indication
36	<i>blister</i>	5	<i>not labeled</i>
37	agitation	5	Adverse Reactions

¹Certain general adverse events that can occur with all drugs are not appropriate to label, such as drug ineffective, medication error, and drug toxicity. These are marked not applicable.

Table 6: Crude Counts and Labeling Status of Adverse Events Reported in at Least 3 (1.7%) of the 172 Pediatric Cases with Serious Outcome Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) (May include duplicates)			
Rank	Preferred Term (PT)	Count	Label Status
1	convulsion	45	Indication
2	rash	19	Black Box Warning
3	Stevens-Johnson Syndrome	18	Warnings
4	drug ineffective	16	not applicable ¹
5	drug exposure during pregnancy	14	not applicable
6	vomiting	13	Adverse Reactions
7	drug interaction	10	not applicable
8	pyrexia	9	Adverse Reactions ("fever")
9	<i>abnormal behavior</i>	8	<i>not labeled</i>
10	irritability	8	Adverse Reactions
11	<i>aggression</i>	6	<i>not labeled</i>
12	diarrhea	6	Adverse Reactions
13	headache	6	Adverse Reactions
14	malaise	6	Adverse Reactions
15	rash maculo-papular	6	Adverse Reactions
16	somnolence	6	Adverse Reactions

¹Certain general adverse events that can occur with all drugs are not appropriate to label, such as drug ineffective, medication error, and drug toxicity. These are marked not applicable.

Rank	Preferred Term (PT)	Count	Label Status
17	tremor	6	Adverse Reactions
18	complex partial seizures	5	Indication
19	drug toxicity	5	not applicable
20	epilepsy	5	Indication
21	toxic epidermal necrolysis	5	Black Box Warning
22	agitation	4	Adverse Reactions
23	alanine aminotransferase increased	4	Adverse Reactions
24	aspartate aminotransferase increased	4	Adverse Reactions
25	<i>blister</i>	4	<i>not labeled</i>
26	<i>candidiasis</i>	4	<i>not labeled</i>
27	<i>coagulopathy</i>	4	<i>not labeled</i>
28	epistaxis	4	Adverse Reactions
29	hepatic enzyme increased	4	Adverse Reactions
30	hypotonia	4	Adverse Reactions
31	ill-defined disorder	4	not applicable
32	insomnia	4	Adverse Reactions
33	lymphadenopathy	4	Warnings (under hypersensitivity reactions)
34	multi-organ failure	4	Warnings
35	overdose	4	Overdosage
36	personality change	4	Adverse Reactions (“personality disorder”)
37	pharmaceutical product complaint	4	not applicable
38	rash generalized	4	Black Box Warning
39	renal failure	4	Adverse Reactions (“kidney failure”)
40	<i>septic shock</i>	4	<i>not labeled</i>
41	viral infection	4	Adverse Reactions (“infection”)
42	<i>abnormal feces</i>	3	<i>not labeled</i>
43	anorexia	3	Adverse Reactions
44	<i>anuria</i>	3	<i>not labeled</i>
45	blood bilirubin increased	3	Adverse Reactions (“bilirubinemia”)

Rank	Preferred Term (PT)	Count	Label status
46	<i>blood pressure decreased</i>	3	<i>not labeled</i>
47	confusional state	3	Adverse Reactions (“confusion”)
48	<i>coordination abnormal</i>	3	<i>not labeled</i>
49	depressed level of consciousness	3	Adverse Reactions (“CNS depression”)
50	disseminated intravascular coagulation	3	Warnings (under Hypersensitivity Reactions) and Adverse Reactions
51	drug dispensing error	3	not applicable
52	dyskinesia	3	Adverse Reactions
53	<i>dysmorphism</i>	3	<i>not labeled</i>
54	dyspnea	3	Adverse Reactions
55	grand mal convulsion	3	Indication
56	hallucination	3	Adverse Reactions
57	hepatic failure	3	Warnings (under Multiorgan Failure)
58	hypersensitivity	3	Warnings
59	<i>hypotension</i>	3	<i>not labeled</i>
60	<i>jaundice</i>	3	<i>not labeled</i>
61	<i>lactose intolerance</i>	3	<i>not labeled</i>
62	lip swelling	3	Warnings (“angioedema”)
63	memory impairment	3	Adverse Reactions (“memory decrease”)
64	<i>mucosal inflammation</i>	3	<i>not labeled</i>
65	nausea	3	Adverse Reactions
66	pain	3	Adverse Reactions
67	pharyngeal edema	3	Warnings (“angioedema”)
68	platelet count decreased	3	Warnings (under Blood Dyscrasias) “thrombocytopenia”
69	rash macular	3	Adverse Reactions (“maculopapular rash”)
70	speech disorder	3	Adverse Reactions
71	visual disturbance	3	Adverse Reactions (“visual abnormality”)
72	weight decreased	3	Adverse Reactions
73	weight increased	3	Adverse Reactions (“weight gain”)

3.5 ADVERSE EVENTS UNDER FOCUS

OPT requested a focus on hepatotoxicity, hypersensitivity reactions, multi-organ failure, blood dyscrasias and rashes. Because lamotrigine labeling describes rash with or without multi-organ involvement and hypersensitivity with or without multi-organ involvement and rash, all cases reporting rash are grouped together and characterized in Table 10. Only cases of hepatotoxicity, hypersensitivity, or blood dyscrasias that did not report rash are described separately from the rash cases. No cases reported multi-organ failure without also reporting rash.

Hepatotoxicity cases were retrieved from AERS by searching with the terms used to search AERS for the OSE December 2006 review of postmarketing reports of hepatotoxicity reported with lamotrigine as a suspect drug.⁸ These MedDRA terms comprise hepatic failure and associated disorders (HLT⁹), hepatic fibrosis and cirrhosis (HLT), hepatic necrosis (PT¹⁰), hepatitis fulminant (PT), liver transplant (PT), hepatitis acute (PT), hepatitis (PT), hepatocellular damage (PT), and hepatotoxicity (PT). The search was limited to reports received by the FDA between May 1, 2006 and August 7, 2008 to retrieve reports entered into AERS since the prior hepatotoxicity review. In addition, MedDRA coding of the 303 reports received during the 1-year post-pediatric exclusivity period was reviewed to identify cases of hepatotoxicity. As with the prior hepatotoxicity review, only cases that did not report rash, hypersensitivity, or multi-organ failure were retained for discussion because liver dysfunction in these contexts is already described in lamotrigine labeling.

Table 7: Reports of Hepatotoxicity in Pediatric Patients Received between May 1, 2006 and August 7, 2008 that Do Not Also Report Rash, Hypersensitivity, or Multi-organ Failure [N=4]	
Report Number Source, Event Date Patient Demographics Outcome	Case Summary
ISR# 5624671 U.S., 2008 12-year-old female Life-threatening	A report with little information states that, after 2.5 years lamotrigine at an unknown dosage to treat bipolar disorder, a 12-year-old female experienced liver failure. Concomitant medical conditions are cerebral palsy and mental retardation.

⁸ Phelan K. Lamotrigine hepatotoxicity. FDA Postmarketing Safety Review. December 29, 2006.

⁹ HLT=MedDRA high level term.

¹⁰ PT=MedDRA preferred term.

<p>ISR# 5249861 Foreign, 2007 13-year-old male Other serious</p>	<p>After 1 month lamotrigine up to 30 mg/day to treat epilepsy, a 13-year-old male experienced increased indirect bilirubin, scleral icterus, nausea, and vomiting. He was diagnosed with Gilbert’s syndrome (familial nonhemolytic jaundice) through genetic testing. Lamotrigine dosage was decreased and the adverse events improved.</p>
<p>ISR# 5397744 U.S., 2007 15-year-old female Other serious</p>	<p>After 7 months lamotrigine up to 100 mg/day to treat depressive anorexia, a 15-year-old female experienced high AST (77 U/L) and ALT (144 U/L) (no reference ranges) and low alkaline phosphatase. The patient had a reactive test for hepatitis B surface antibody. Lamotrigine dosage was decreased and the adverse events improved. Concomitant medications were sertraline and ibuprofen.</p>
<p>ISR# 5409725 Foreign, 2006 8-week-old male Hospitalized</p>	<p>A male neonate exposed to lamotrigine in utero and via breast milk developed conjugated hyperbilirubinemia, cholestasis, and hepatitis. He had been jaundiced from birth. Bilirubin declined “dramatically” over a few days when breast feeding was discontinued. Phenotyping revealed alpha₁-antitrypsin deficiency.</p>

Table 8: Reports of Hypersensitivity Reactions in Pediatric Patients Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) that Do Not Also Report Rash [N=1]

<p>Report Number Source, Received Date Patient Demographics Outcome</p>	<p>Case Summary</p>
<p>ISR# 5614153 U.S., 2008 15-year-old female Hospitalized</p>	<p>On the day following her first dose of lamotrigine 25 mg to treat mood disorder, a 15-year-old female experienced tremor, inability to breathe, and syncope. She was nonresponsive and was hospitalized in intensive care. The following day, she became responsive but experienced unspecified speech difficulty and sore throat. All lab work was normal. The physician suspected allergic reaction. There were no concomitant medications.</p>

Table 9: Reports of Blood Dyscrasias in Pediatric Patients Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) that Do Not Also Report Rash [N=6]

Report Number Source, Received date Patient Demographics Outcome	Case Summary
ISR# 5402712 foreign, 2007 6-year-old male Hospitalization	After 3-months lamotrigine at an unknown dosage to treat seizure, a 6-year-old male experienced hematemesis. Activated partial thromboplastin time was increased. Patient was hospitalized, treated with frozen blood plasma and recovered. He was being tapered off lamotrigine at the time of reporting. Concomitant medication was valproic acid.
ISR# 5250578 U.S., 2007 9-year-old male Hospitalization	After 1-year lamotrigine 125 mg/day to treat epilepsy, a 9-year-old male developed neutropenia with an absolute neutrophil count less than 500 (no units). Patient was hospitalized. Red blood cell, white blood cell, and platelet counts were normal an unspecified time before lamotrigine use. Concomitant medications were zonisamide, carnitine, phenobarbitone, famotidine, baclofen, and thiamine, all with unknown timing. Zonisamide labeling has a warning that includes agranulocytosis. Concurrent medical condition was unspecified metabolic disorder.
ISR# 5556827 U.S., 2007 16-year-old female Hospitalization	A report with little information states that a 16-year-old female experienced acute renal failure, sudden onset fever of 104 F, and an unspecified blood dyscrasia which prolonged hospitalization during titration of lamotrigine, at 75 mg/day.
ISR# 5416727 Foreign, 2007 11-year-old male No adverse event	After 2 months lamotrigine up to 50 mg/day to treat mood disorder, an 11-year-old male hit his head against a wall causing nosebleed. Because the bleeding seemed to last longer than usual, tests were done that showed prolonged partial thromboplastin time, low prothrombin index, and hypochromic microcytic anemia. Blood samples sent to other laboratories found no abnormalities and the abnormal results were considered to be caused by lab error. Lamotrigine continued and the patient recovered.

Report Number Source, Received date Patient Demographics Outcome	Case Summary
ISR# 5250208 U.S., 2007 13-year-old male Other serious	After 3 months lamotrigine up to 100 mg/day to treat bipolar disorder, a 13-year-old male experienced neutropenia with neutrophil count decreased from 1.1 to 0.8 and white blood count of 4.7 (no units). Concurrent medications were valproic acid and Adderall. Lamotrigine continued and the event was unresolved at the time of reporting. Valproic acid labeling lists agranulocytosis under Adverse Events.
ISR# 5474205 Foreign, 2004 9-year-old female Hospitalization	After 2 years lamotrigine at an unknown dose to treat epilepsy, a 9-year-old female developed atopic eczema. Three months later, she developed bleeding and aplastic anemia and was hospitalized. She then developed bone marrow failure and was treated with blood transfusions every 4 to 7 days for over a year. The patient was also treated with antithymocyte immunoglobulin, methylprednisolone, and cyclosporin for the adverse event. At the time of reporting, bone marrow failure was unresolved. Concomitant medication was ethosuximide, started 4 months before aplastic anemia developed. Ethosuximide labeling carries a warning for blood dyscrasias and bone marrow suppression is listed as an adverse event.

The following table summarizes the characteristics of the 104 reports of rash among the 303 pediatric reports received during the pediatric exclusivity period. Characteristics were extracted from aggregate AERS data, not from hands-on case review, and so, may contain duplicates.

Table 10: Characteristics of AERS Reports of Rash in Pediatric Patients Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) [N=104; May include duplicates]			
Gender [n=101]	Male (41) Female(60)		
Origin [n=104]	US (83), Foreign (21)		
Event date [n=77]	1996 (1)	2005 (6)	2007 (20)
	2004 (2)	2006 (47)	2008 (1)

MedDRA-coded adverse events reported in two or more reports [n=104]
Not mutually exclusive.

Skin/Mucus Membranes

- rash / rash generalized / urticaria / skin lesion / rash maculo-papular / rash erythematous / dermatitis bullous / drug eruption / erythema (89)
- Stevens-Johnson syndrome (18)
- toxic epidermal necrolysis (5)
- skin exfoliation / skin erosion / exfoliative rash (8)
- skin hemorrhage / petechiae (4)
- genital erosion (2)
- mucosal inflammation (3)
- lip erosion / lip exfoliation / lip swelling (6)
- pruritis (6)
- blister (5)

Hematological

- thrombocytopenia / platelet count decreased (5)
- coagulopathy (3)
- disseminated intravascular coagulation (3)
- leukocytosis (2)
- anemia (2)
- eosinophilia (2)
- pancytopenia (2)

Infection

- sepsis / septic shock (6)
- viral infection (3)
- upper respiratory tract infection (2)
- candidiasis (4)

Hypersensitivity

- drug hypersensitivity / hypersensitivity (5)
- drug rash with eosinophilia and systemic symptoms (2)

Renal

- renal failure (4)
- anuria (3)

Respiratory

- respiratory distress / acute respiratory distress syndrome (4)
- pharyngeal edema (3)
- epistaxis (3)

Gastrointestinal

- vomiting /nausea / diarrhea (7)
- lactose intolerance (3)
- anorexia (2)
- abnormal feces (3)

	<p>Hepatic</p> <ul style="list-style-type: none"> • hepatic failure (2) • hepatocellular injury (2) • hepatosplenomegaly (2) • ALT increased / AST increased / hepatic enzyme increased (9) <p>General</p> <ul style="list-style-type: none"> • multi-organ failure (4) • pyrexia / hyperthermia (11) • upper limb fracture (2) • convulsion (6) • hypotension (3) • pain (4) • headache (4) • malaise (4) • asthenia (2) • lymphadenopathy (3) • local swelling (2) • medication error (2) • drug ineffective (4) • drug interaction (2)
Most serious outcome selected on MedWatch form [n=62]	Death (0), Life-Threatening (8), Hospitalization (23), Required Intervention (0), Disability (1), Congenital Anomaly (4), Other Serious (26)

**Table 6: Crude Counts of Respiratory Illness or Infection Adverse Events Reported in the 303 Pediatric Cases Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008)
(May include duplicates)**

Rank	Preferred Term (PT)	Count
1	viral infection	5
2	candidiasis	4
3	dyspnea	4
4	pharyngeal edema	3
5	pharyngolaryngeal pain	3
6	acute respiratory distress syndrome	2
7	aspiration	2
8	cough	2
9	infection	2
10	respiratory distress	2
11	respiratory rate increased	2
12	upper respiratory tract infection	2
13	bronchostenosis	1
14	influenza	1
15	nasopharyngitis	1
16	pharyngitis	1
17	rhinitis	1
18	superinfection	1
19	wheezing	1

The reports of acute respiratory distress syndrome and respiratory distress syndrome also report Stevens Johnson syndrome. The case reporting bronchostenosis is an in utero exposure case. The three reports of pharyngeal edema are duplicates of one case that also reports rash, respiratory infection, and chronic Candida infection that requires a restricted anticandida diet.

3.6 IN UTERO EXPOSURES TO LAMOTRIGINE

Table 11: Characteristics of In Utero Exposure Cases Received During the Pediatric Exclusivity Period (February 14, 2007 to March 14, 2008) [N=18, duplicates removed]			
Gender [n=15]	Male (8) Female(7)		
Origin [n=18]	US (5), Foreign (13)		
Event date [n=15]	1997 (1) 2003 (1)	2005 (2) 2006 (4)	2007 (7)

Reported adverse events [n=18] Not mutually exclusive.	Exposure to lamotrigine in breast milk (3) Jaundice (3) Fetal anticonvulsant syndrome (2) Multiple malformations (2) Delayed motor milestones (2) Gastroesophageal reflux (2) Hypoglycemia (2) Sudden infant death (1) Hypertonia and jitteriness attributed to lamotrigine withdrawal (1) Intrauterine growth retardation (1) Infantile spasms (1) Gut malrotation (1) Neutropenia (1) Neonatal adaptation disorder (1) Foramen ovale persistence and peripheral pulmonary stenosis (1) Cholestasis, hepatitis, and alpha-1 anti-trypsin deficiency (1) Tooth enamel disorder (1) Facial palsy (1) Facial dysmorphism, tongue extrusion, and mild epicanthus (1) Cleft palate and suspected Pierre-Robin syndrome (1) Cleft lip and palate (1) Amelia of lower limb, unilateral (1) Neonatal axial hypotonia (1) Syndactyly, bilateral (1) Juvenile rheumatoid arthritis (1) Lamotrigine detected in infant's blood (1)
Concomitant exposures [n=12] Not mutually exclusive.	valproic acid (3) levetiracetam (1) ranitidine (1) thyroid medicine (1) folic acid / vitamins (3) none (3)
Outcomes as reported in narratives [n=16] Not mutually exclusive.	Death (1), Life-Threatening (0), Hospitalization (6), Required Intervention (2), Disability (5), Congenital Anomaly (7)

3.7 DEATHS SINCE APPROVAL (N= 83)

From lamotrigine approval in 1994 to the AERS search date of June 23, 2008, FDA received 106 reports of death in pediatric patients that list lamotrigine as a suspect drug. Hands-on review of these cases and elimination of duplicate reports revealed 83 unique cases.

Table 12: Characteristics of Pediatric Cases Reporting an Outcome of Death Received From Lamotrigine Approval (December 27, 1994) to the AERS Search Date (June 23, 2008) [N=83, duplicates removed]				
Gender [n=74]	Male:	(38)		
	Female:	(36)		
Age [n=82]	0-<1 month	(8)		
	1 month-<2 yrs	(7)		
In addition, there was one therapeutic abortion reported.	2-5 yrs	(20)		
	6-11 yrs	(28)		
	12-16 yrs	(19)		
	Median 7 years; Range birth to 16 years			
Origin [n=81]	US (23), Foreign (58)			
Event date [n=68]	1993 (1)	1998 (1)	2002 (6)	2006 (2)
	1995 (5)	1999 (7)	2003 (8)	2007 (2)
	1996 (6)	2000 (4)	2004 (3)	2008 (1)
	1997 (6)	2001 (9)	2005 (7)	
Daily dose [n=57] (plus 11 in utero)	Mg/day [n=54]: Average 140, Median 75, Range 2.5 to 900			
	Mg/kg/day [n=3]: Average 9.5, Median 8.5, Range 5 to 15			
Duration of therapy [n=58]	Median 1.5 months			
	Range 2 days to 5 years			
Indications [n=62]	Epilepsy/seizures/convulsions (56)			
	Lennox-Gastaut Syndrome (3)			
	Bipolar disorder (2)			
	Cerebral cysts (1)			
Primary adverse event or cause of death [n=83] (mutually exclusive)	Seizure/ prolonged seizure/status epilepticus (19)			
	Found dead / death / sudden death (19)			
	Rash / Stevens Johnson syndrome / toxic epidermal necrolysis (16)			
	Prematurity / congenital anomalies / complications of birth (8)			
	Therapeutic abortion of fetus with neural tube defects (1)			
	Pneumonia / pulmonary infection / aspiration pneumonopathy (4)			
	Sepsis (1)			
	Varicella infection (1)			
	MELAS syndrome progression (1)			
	Alexander's syndrome (genetic leukodystrophy) (1)			
	Fall and fracture skull and neck (1)			
	Hit by truck (1)			
	Cardiac arrest / cardiac insufficiency / cardiomyopathy / acute myocarditis (4)			
	Cardiac and respiratory failure (1)			
	Cerebrovascular disorder and hepatic abnormality (1)			
	Respiratory arrest (1)			
	Liver failure (1)			
	Renal failure (1)			
	Hemorrhagic pancreatitis (1)			

The majority of the adverse events associated with death in these cases are expected complications of epilepsy or are labeled warnings and precautions for lamotrigine. These include seizures, sudden death, and serious rashes with organ failure. For several other reported causes of death, such as premature birth or congenital anomalies, infection, accident, or disease progression, lamotrigine use cannot be excluded as a contributing factor. However, the small numbers of these events does not support lamotrigine association at this time.

Several of the adverse events reported in cases resulting in death do invite closer attention. These cases are summarized below:

- Cardiomyopathy – After 4.5 years lamotrigine monotherapy, a 10-year-old male was found unconscious. He could not be revived. Autopsy showed signs of heart muscle disease, blood congestion, and lymphatic-tissue changes. (ISR# 3902298)
- Cardiac arrest – A report with little information states that a 16-year-old patient experienced cardiac arrest 1 month after initiating lamotrigine and oxcarbazepine for unknown indications. He was hospitalized and died 1 week later. Concomitant drugs were diazepam and clobazam. (ISR# 4222413, 4218076)
- Acute myocarditis – A 13-year-old male experienced increasing seizures over 3 years lamotrigine treatment. Topiramate was added. Two months later, he was taken to the emergency room and admitted to the hospital for an unspecified reason. He died suddenly and autopsy found acute myocarditis. (ISR# 4715158)
- Cardiac insufficiency – Six months after initiating lamotrigine to treat epilepsy, an 8-year-old female was found dead. Autopsy found cardiac insufficiency and generalized inflammation of the respiratory tract. The public prosecutor is investigating the death. (ISR# 4209789)
- Respiratory and cardiac failure – A 3-year-old male with encephalopathy and long-term oxygen treatment developed respiratory and cardiac failure after taking lamotrigine for 18-months. Concomitant drugs were valproic acid and trichloroacetaldehyde. (ISR# 3003267)
- Respiratory arrest – A 4-year-old male developed fever and vomiting, reported as flu, after 1.5 months lamotrigine to treat seizures. The following morning, he had a 30-minute seizure. That evening, he stopped breathing and died. Concomitant medications were valproic acid, phenytoin, and melatonin. Concomitant medical condition was global developmental delay. (ISR# 1722423)
- Cerebrovascular disorder and hepatic abnormality – A report with little information states that, after about 1 year valproate sodium and 2 weeks lamotrigine to treat epilepsy, a 1-year-old male developed unspecified cerebrovascular disorder, hepatic abnormality, and purpura. He was hospitalized and died a few weeks later. (ISR# 3142607, 3182342)
- Liver failure – A 15-year-old female experienced rash and discontinued lamotrigine after 3 weeks treatment for blackouts. The rash resolved, blackouts continued, and she developed occasional vomiting. Phenobarbital was started and, 2 days later, 2.5 weeks after lamotrigine was stopped, she was diagnosed with liver failure. A few

days later, brain edema and death occurred. Reye's syndrome was questioned. (ISR# 4895225)

- Renal failure – Amphotericin and acyclovir, both associated with renal failure, were started 2 days before adverse event onset in a multiply-handicapped, 10-year-old male who had been taking lamotrigine for 10 months. (ISR# 4635175)
- Hemorrhagic pancreatitis – After 2 years lamotrigine and about 2 months topiramate, an 8-year-old female developed hemorrhagic pancreatitis and died within 20 hours. (ISR#4080303)

PharmaPendium¹¹ searches of lamotrigine NDA packages for cardiac adverse events in humans found no drug-related cardiac adverse events outside of the context of status epilepticus, multi-organ failure, or rash.¹² Animal data, described in the label, showed electrocardiogram changes associated with a lamotrigine metabolite in dogs, but the metabolite, 2-N-methyl lamotrigine, has been seen only in trace amounts in humans.

4 DISCUSSION

Lamotrigine has been labeled for use in pediatric patients for 10 years and, specifically, in patients aged 2 years and older for 5 years based on controlled clinical trials. Overall, the percentages of domestic AERS reports received during the pediatric exclusivity period for patients aged 0 through 1 year, 2 through 5 years, 6 through 11 years, and 12 through 16 years are comparable to the estimated usage in these age groups during approximately the same time period. Estimated usage is based on projected numbers of patients receiving prescriptions for lamotrigine dispensed by U.S. retail pharmacies per Verispan Vector One National usage data.¹³ Thus, adverse event reporting in pediatric patients in the U.S. is proportional to lamotrigine prescriptions dispensed for pediatric patients in the U.S.

Lamotrigine pediatric adverse event reporting in 2007, the year encompassing most of the pediatric exclusivity period, was higher than in preceding years. However, the increase appears to be the continuation of a trend that began in 2003, when lamotrigine was approved as adjunctive treatment for partial seizures, and unrelated to pediatric exclusivity.

Characteristics of the 303 pediatric AERS reports received during the pediatric exclusivity period show most patients to be in the age group for which lamotrigine is indicated, with fairly even distribution between males and females. Bipolar disorder and other emotional disorders are substantial off-label uses in the adverse event reports.

¹¹ PharmaPendium™ is an Elsevier product that contains indexed and searchable drug information including FDA drug approval packages.

¹² NDA 20-241 FDA Approval Package Medical/Clinical Review 10/14/1994, and NDA 20-764 FDA Approval Package Medical/Clinical Review 3/7/1997.

¹³ Projected number of patients receiving a prescription for lamotrigine dispensed by U.S. retail pharmacies March 2007 through February 2008. Source: Verispan Vector One: National, Extracted 6-2008, 2007-388 TPT Lamotrigine.

Lamotrigine is labeled to treat bipolar disorder in adults, however, so this use in pediatric patients is not unexpected.

Adverse events reported in pediatric reports with serious outcomes received during the pediatric exclusivity period do not raise new concerns. The adverse events coded in more than 3 of the 172 reports with serious outcomes differs from those coded in more than 5 of the 303 total pediatric AERS reports for the pediatric exclusivity period primarily in including events that are not specifically labeled but are signs or symptoms of labeled events. For example, anuria is not labeled but kidney failure is labeled. Coagulopathy is not labeled but thrombocytopenia and disseminated intravascular coagulation are labeled. Likewise, abnormal feces and jaundice are not labeled, but hepatotoxicity is labeled in specific contexts.

All of the adverse events under focus at the request of OPT are labeled events with the possible exception of hepatotoxicity. “Hepatic abnormalities” is labeled in the contexts of rash and hypersensitivity under Warnings. “Various degrees of hepatic failure” is labeled in the context of acute multi-organ failure under Warnings. “Hepatitis” is labeled under Adverse Reactions. The other adverse events under focus, hypersensitivity reactions, multi-organ failure, blood dyscrasias, and rashes, all appear as subsections under Warnings.

Of the four pediatric hepatotoxicity cases that did not report hypersensitivity, multi-organ failure, or rash, two reported diagnoses of genetic conditions that could account for the observed hepatic abnormalities. One patient was diagnosed with Gilbert’s syndrome and the other with alpha₁-antitrypsin deficiency. The remaining two cases do not provide information such as concomitant medications or tests to rule out causes other than lamotrigine. However, neither provides an alternate explanation for the observed hepatotoxicity and one calls the event life-threatening liver failure. Overall, the cases resemble those identified in the December 29, 2006 OSE review of hepatotoxicity with lamotrigine. That review concluded that hepatotoxicity without overt signs of rash, hypersensitivity, or multi-organ failure had been reported in patients taking lamotrigine. The sponsor was subsequently asked to periodically review the issue of hepatotoxicity with lamotrigine.

The one case reporting allergic reaction, but not rash, reports inability to breathe and syncope. Neither of these adverse events is described under hypersensitivity in lamotrigine labeling. However, in the Adverse Events section, lamotrigine labeling lists angioedema, an allergic reaction which can produce inability to breathe and syncope.

All of the blood dyscrasias reported in pediatric patients during the pediatric exclusivity period in cases that do not also describe rash are listed in the Warnings section of lamotrigine labeling. In the Warnings section, lamotrigine labeling lists neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, aplastic anemia, and pure red cell aplasia under the heading Blood Dyscrasias. In addition, one of the six cases is attributed to laboratory error, three include confounding concomitant drug use, and two are lacking important information. The three cases with concomitant labeled drugs include one report of aplastic anemia temporal to ethosuximide, which lists blood dyscrasias in Warnings and bone marrow suppression in Adverse Events sections of labeling. The other two report neutropenia and concomitant zonisamide or valproic acid use with

unknown timing. Zonisamide labeling carries a warning for agranulocytosis; valproic acid labeling lists agranulocytosis under Adverse Events. One of the six blood dyscrasia cases reports renal failure and an unspecified blood dyscrasia. Renal failure is labeled for lamotrigine, but without a more specific description, the labeling status of this blood dyscrasia cannot be determined. The remaining case among the six reports increased activated partial thromboplastin time but no cause for this laboratory abnormality. Thus, no blood dyscrasias requiring additional review were found.

Lamotrigine labeling describes life-threatening rashes with possible multi-organ involvement, including hepatic failure, in a Black Box Warning, a bolded warning, and a precaution. Furthermore, labeling states that the incidence of such rashes in clinical trials was greater in pediatric than in adult patients. None of the rash cases reported in pediatric patients during the pediatric exclusivity period had an outcome of death. The rash cases in this review present a profile that is in keeping with labeling.

OPT also expressed particular interest in the issue of increased incidence of respiratory illness or infection in pediatric patients receiving lamotrigine. According to lamotrigine labeling, infection, bronchitis, and flu syndrome were seen in more than 5% of pediatric patients who received adjunctive lamotrigine in clinical trials for epilepsy. These adverse events occurred at a lower, unspecified, rate in the placebo group. For events with low background rates and known association with drug use, such as serious skin reactions, AERS reporting rates can sometimes provide evidence of association with a particular drug. However, for high-background events, such as respiratory infections, AERS data are not generally helpful in determining drug-event associations. Nor can AERS data be used to calculate incidence rates. Therefore, AERS cannot be used to assess a possibly increased rate of respiratory illness or infection in pediatric patients. For this review, pediatric respiratory adverse events reported in the pediatric exclusivity period were searched for unusual, that is, low-background, adverse events. Respiratory distress, bronchostenosis, and pharyngeal edema were found in the contexts of Stevens Johnson syndrome, in utero exposure, and chronic Candida infection, respectively. Thus, all of these unusual respiratory adverse events could be secondary to other factors in each of the cases.

The pediatric exclusivity period included 18 cases of in utero lamotrigine exposure. The adverse events reported do not show any pattern of events nor do they include any highly unusual birth outcomes. Thus, no specific signal of fetal harm that could be illuminated using AERS data was revealed by these cases. Drug pregnancy registries are better suited to investigating pregnancy outcomes with drug exposure.

Hands-on review of all AERS reports of death in pediatric patients since lamotrigine approval found 83 unique cases. Contrary to the preponderance of U.S. AERS lamotrigine reports over all, 58 of the 83 cases of death in pediatric patients were received from foreign sources. The majority of the adverse events associated with death in these cases are expected complications of epilepsy or are labeled warnings and precautions for lamotrigine. These include seizures, sudden death, and serious rashes with organ failure. For several other reported causes of death, such as premature birth or congenital anomalies, infection, accident, or disease progression, lamotrigine use cannot be excluded as a contributing factor, but these adverse events also occur in the absence of drug use. Therefore, their occurrence does not suggest drug-relatedness without

additional data, such as incidence rates. Indications for use in 59 of the 62 cases reporting indication are labeled pediatric indications.

Among the cases of death that do not fit into the categories described in the preceding paragraph and that are individually summarized in section 3.7 of this review, one report each of liver failure, renal failure, and hemorrhagic pancreatitis were temporal to other drugs. Two additional cases, reporting respiratory failure and arrest, both contain suggestions of complexity that make them less suggestive of lamotrigine as a primary cause. In one case, the patient had been on long-term oxygen treatment and, in the other case, the patient had other signs of illness and a prolonged seizure hours before respiratory arrest occurred.

Four of the summarized death cases report cardiac adverse events, reported as heart muscle disease, acute myocarditis, and cardiac insufficiency, all documented on autopsy, and cardiac arrest. The case of cardiac arrest was temporal to initiation of oxcarbazepine as well as lamotrigine and the case of acute myocarditis was temporal to initiation of topiramate. However, the cases of cardiomyopathy and cardiac insufficiency, while not detailed, do not report confounding factors. Also, they are similar in that both occurred in pre-adolescent children who had taken lamotrigine for 6 months or longer. These two cases included extra-cardiac adverse effects of generalized respiratory tract inflammation in one case, and lymphatic tissue changes in the other. Both cases are rather nonspecific in their descriptions of the adverse events, but the overall impression is of a similarity that could possibly signal an adverse effect of chronic lamotrigine treatment on cardiac and perhaps other tissues. To explore this issue, the NDA review packages¹⁴ were searched using PharmaPendium¹⁵ for cardiac effects. Cardiac adverse events in humans that were thought to be drug-related were not found, except in the context of status epilepticus, multi-organ failure, or rash. Cardiac effects in animal studies were limited to electrocardiogram changes attributed to a lamotrigine metabolite that occurs in much lower concentrations in humans. The cardiac adverse event cases found in this review, in the absence of other evidence, are not sufficient to support a full review of the issue at this time.

CONCLUSION

Overall, the adverse event profile of lamotrigine in the 1-year pediatric exclusivity period and in pediatric deaths since lamotrigine approval is in keeping with lamotrigine labeling. One potential signal of an insufficiently labeled adverse event is described in this review, however. A signal for hepatotoxicity was identified prior to this review and AERS data for all ages since lamotrigine approval were reviewed in December 2006. That review concluded that there were reports of hepatotoxicity that did not also describe rash or multi-organ failure, the contexts in which hepatotoxicity is labeled. This pediatric review supports that conclusion and does not change the overall impression of the hepatotoxicity

¹⁴ NDA 20-241 FDA Approval Package Medical/Clinical Review 10/14/1994, and NDA 20-764 FDA Approval Package Medical/Clinical Review 3/7/1997.

¹⁵ PharmaPendium™ is an Elsevier product that contains indexed and searchable drug information including FDA drug approval packages.

issue. Hepatotoxicity with lamotrigine has been discussed with the sponsor and they have been asked to review the issue.

RECOMMENDATIONS

This review of adverse events with lamotrigine in pediatric patients in the 1-year pediatric exclusivity period found no previously unknown adverse events in pediatric patients. Outcomes of adverse events analyzed in this review conform to those that have been previously identified and labeled. Therefore, continuation of routine post-marketing adverse event monitoring is recommended.

signed September 30, 2008

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Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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